REMARKS

Claims 51-58 were pending in the application. Claims 52, 54 and 58 have been cancelled. Claims 51, 53, 55 and 56 have been amended. New claims 59 and 60 have been added. Accordingly, claims 51, 53, 55-57, 59 and 60 are now pending.

Support for the amendment to claim 51 can be found in the specification, at least at page 29, lines 8-24. Claim 53 has been amended to correct sequence reference and to correct dependency of the claim. Claim 55 has been amended to correct dependency of the claim. Support for the amendment to claim 56 can be found in the specification at least at page 29, line 20 through page 30, line 5. Support for new claim 59 can be found in the specification at least at page 29, lines 10-15. Support for new claim 60 can be found in the specification at least at page 47, lines 16-21 and page 62, line 30 through page 63, line 14. No new matter has been added.

Amendments to the claims should in no way be construed as acquiescent to any of the Examiner's rejections and were made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 51-58 Under 35 U.S.C. § 112, First Paragraph, Written Description

The Examiner has rejected claims 51-58 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that Applicants had possession of the invention at the time the application was filed. The Examiner states,

> [T]here does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides coverage for the broad class of sequences or molecules encompassed by the term soluble lymphotoxin beta receptor or functional sequence of amino acids selected from the amino acids of SEQ ID No: 1, because the claims fail to provide for specific functional language that can be correlated to the genus of molecules claimed.

The Examiner also states that "[w]ith the exception of SEQ ID NO: 1, the skilled artisan cannot envision the detailed structure of the encompassed polypeptide or fragments of the polypeptide variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." In reference to the heterologous protein constructs of the present invention, the Examiner

further states, "In the case of the heterologous proteins, the specification has only described an immunoglobulin Fc portion conjugated to the sLTβR molecule and therefore, the Applicant has not provided sufficient evidence that they were in possession of the invention as claimed." Applicants respectfully traverse this rejection.

As amended, claim 51 is directed to a method of treating systemic lupus erythematosus (SLE) in a mammal by administering a pharmaceutical composition comprising an effective amount of a soluble lymphotoxin-beta receptor (LTβR) comprising at least one ligand binding domain that can selectively bind to a surface LT ligand fused to one or more heterologous protein domains. Applicants' specification provides ample disclosure for one of ordinary skill in the art to identify the composition of such an agent. The present application teaches treatment of SLE in a mammal *via* administration of soluble LTβR agents. Both the specification and claim 51 as amended make clear that a functional soluble LTβR agent of the invention is one that contains at least one ligand binding domain of LTβR (refer to the present specification, at least at page 32, lines 23-27). As defined in the specification at page 14, lines 20-23, "[t]he term "LTβ-R ligand binding domain" refers to the portion or portions of the LTβ-R that are involved in specific recognition of and interaction with a LT ligand." At page 15 of the present specification, Applicants additionally have described the TNF family of ligands and their associated receptors, to which surface LT and the LTβR respectively belong, and have indicated that the topology and functional domains of LTβR were known to one of ordinary skill in the art at the time of filing. (Indeed, characterization of the sequence and functional domains of human and mouse LTβR were performed by Crowe et al. (Reference CL of the IDS) and Force et al. (Reference CU of the IDS), both referenced by the present specification.)

At page 29 of the instant specification, Applicants further teach how to produce the soluble LTβR molecules of the present invention. Applicants present the sequence of the extracellular portion of human LTβR in Figure 1 of the instant application and describe this sequence as containing the ligand binding domain of LTβR. The present specification at page 30, lines 1-5 additionally states that "[a]ll or a functional portion of the LTβ-R extracellular region (Figure 1) comprising the LTβ-R ligand binding domain may be fused to an immunoglobulin constant region like the Fc domain of a human IgG1

heavy chain [Reference CH of the IDS]." Based on the descriptive sections of the specification and the state of the art at the time, one of ordinary skill in the art would be capable of envisioning the full scope of the claimed soluble forms of LTβR.

Applicants additionally describe the use of two separate forms of soluble LTβR as working examples within the present specification. Examples 1 and 2 of the present specification (refer to pages 58-60) detail the synthesis of human and murine soluble LTβR agents, respectively. The murine soluble LTβR-Ig molecule was then employed in Examples 3-7 of the present specification. The human and murine soluble LTβR agents featured in the instant invention were additionally described in Applicants' previously co-pending 08/505,606 application (now the '351 patent; refer to page 29, line 18 of the present specification), as well as in Browning et al. (Reference CH of the IDS). At page 31, lines 15-31 of the instant specification, Applicants further describe deposit in the American Type Culture Collection (ATCC) of distinct CHO cell lines that secrete soluble human LTβR-Fc and soluble murine LTβR-Ig fusion proteins, respectively. Thus, at the time of filing, Applicants were additionally in possession of working examples of presently claimed agents comprising soluble LTβR fused to a heterologous protein domain.

In light of both the state of the art and the teachings of the specification, one of ordinary skill in the art additionally would have recognized Applicants to be in possession of the genus encompassed by "a soluble lymphotoxin-beta receptor (LTβR) comprising a ligand binding domain that can selectively bind to a surface LT ligand fused to one or more heterologous protein domains", as presently claimed. Indeed, the topology and functional domains of LTβR were known to one of ordinary skill in the art, as described in the present specification. Having knowledge of the LTβR sequence (SEQ ID NO: 1 of the present specification) and ligand binding domain structure of LTβR, one of ordinary skill in the art at the time of filing would have recognized Applicants' possession of soluble forms of LTβR as encompassing the full scope of soluble forms of LTβR molecules that comprise at least one intact ligand binding domain. Thus, there is sufficient description in the specification as well as knowledge in the art at the time of filing to convey to one of ordinary skill in the art that Applicants were in possession of the soluble LTβR agents of the presently claimed invention.

The present specification also demonstrates that Applicants were in possession of the presently claimed soluble LTβR agents fused to one or more heterologous protein domains. Methods of generating fusion proteins were widely known to those of ordinary skill in the art at the time of filing, and Applicants' specification at page 29, lines 29-30 teaches "immunoglobulins, serum albumin, lipoproteins, apolipoproteins, and transferrin" as exemplary components of soluble LTβ-R fusion proteins. These components were widely recognized to one of ordinary skill in the art at the time of filing as stable plasma proteins. One of ordinary skill in the art also would have been aware of art-recognized cell and tissue type-specific protein domains. Provided Applicants' disclosure, one of ordinary skill in the art would therefore recognize that one could fuse soluble LTβR to such domains for practice of the instant invention as described in the specification (see page 29, lines 30-33). Thus, the present written description does much more than "only describe . . . an immunoglobulin Fc portion conjugated to the sLTβR molecule", as the Examiner asserts. Indeed, Applicants' written description supports the present scope of the claims as they relate to the heterologous proteins of the invention, since the present specification, when combined with the knowledge of one of ordinary skill in the art, would not have led one of skill in the art to question Applicants' possession of heterologous sLTβR molecules to the full extent of those fusion proteins that are presently claimed.

As the Examiner is aware, according to the PTO's own written description guidelines, the written description requirement does *not* require that a representative number of species of a claimed genus be "reduced to practice" but rather, simply requires that a representative number be disclosed. Indeed, there is no basis in the law to require Applicants to provide *any* working examples to satisfy the written description requirement (though Applicants have provided such working examples in the present specification). Furthermore, "a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (see MPEP 2163(II.A.3.a.ii). Here, Applicants have, in fact, fully disclosed their possession of two working examples of soluble LTβR fusion proteins and have described the scope of compositions encompassed by the term "soluble lymphotoxin-beta receptor (LTβR) fused to one or more heterologous protein domains" in the present written description. Applicants' teachings, in

combination with the advanced state of the art with respect to synthesis of fusion proteins at the time of filing, would have conveyed to one of ordinary skill in the art that Applicants were in possession of the invention as presently claimed. Applicants therefore submit that the written description requirement set forth in 35 U.S.C. 112, first paragraph is satisfied and the Examiner is requested to reconsider and withdraw this rejection.

Rejection of Claims 51-58 Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner has rejected claims 51-58 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that "the specification is devoid of teaching how one of skill in the art is to use the instant method for treating, prevention or elimination of SLE." Applicants respectfully traverse this rejection.

Solely to expedite the prosecution of the application, claim 51 has been amended to read, "[a] method of **treating** systemic lupus erythematosus (SLE) in a mammal comprising administering a pharmaceutical composition comprising a therapeutically effective amount of a soluble lymphotoxin-beta receptor (LTβR) fused to one or more heterologous protein domains and a pharmaceutically acceptable carrier" (emphasis added). Within the present specification, Applicants have demonstrated that administration of soluble LTβR-Ig disrupts splenic marginal zone architecture, thereby dramatically impacting antibody response in LTβR-Ig-treated mice. Specifically, Applicants have shown that splenic germinal centers (GCs) failed to form in mice treated with LTβR-Ig. In addition, a dramatic impact on follicular dendritic cell (FDC) phenotype in LTβR-Ig-treated mice was observed. As a result of the disruption of FDC phenotype and GC formation, the humoral immune response (antibody response) of the LTβR-Ig-treated mice was dramatically compromised (both IgG and IgM responses were diminished in LTβR-Ig-treated mice relative to mock-treated mice).

As of the priority date of the present application, SLE was recognized by those skilled in the art to be an antibody-mediated autoimmune disease in which disease progression correlates with the presence of affinity-matured anti-dsDNA antibodies (Shlomchik et al., (1990) J. Exp. Med. 171: 265-97; enclosed as Appendix A). Affinity maturation of antibodies had also been characterized to occur in GC cells, with a critical step in the process featuring the binding of high-affinity B cells to FDCs within the GC (reviewed in Lindhout E and de Groot C, (1995) Histochem. J. 27: 167-83; enclosed as Appendix B). Thus, proper FDC and GC function had

been recognized as of the priority date of the present application as necessary for SLE disease progression. Therefore, in view of Applicants' demonstrated effect on disruption of FDC phenotype and GC development in the spleen and lymph nodes of LTβR-Ig-treated mice, one of ordinary skill in the art would have reasonably expected to successfully use soluble forms of LTβR to treat a subject with SLE.

Applicants respectfully submit that the Examiner has misinterpreted Applicants' experiments described in the present specification. Specifically, Applicants did not employ "an immunodeficient SCID mouse" in the examples of the present specification, as stated by the Examiner, but instead examined splenic architecture and response to immune challenge in soluble LTβR-treated and untreated healthy mice (e.g., Balb/c mice). The Examiner has also incorrectly characterized this mouse model of SLE as "an atypical or unconventional model for the examination of SLE." The model of SLE which Applicants describe is that of the art-recognized (SWR x NZB)F_1 (SNF_1) mouse model of fatal lupus nephritis previously utilized by Mohan *et al* (Reference CAY of the IDS) to study the effect of CD40/CD40 ligand blocking agents. While the induced, anti-DNA antibody mouse models of SLE (*e.g.*, Mendlovic *et al*) the Examiner has cited were also known in the art at the time of filing, the Examiner has incorrectly concluded that such induced models encompassed all art-recognized models of SLE. In contrast, as described by Applicants, art-recognized models of SLE included spontaneously arising models, such as the one described by Mohan *et al*. Thus, one of ordinary skill in the art would have recognized that efficacy in such models would be predictive of efficacy in the treatment of SLE.

Thus, based on the teachings of the specification in combination with the knowledge in the art at the time of Applicants' priority filing regarding the role of splenic architecture and antibody response in SLE, one of ordinary skill in the art would reasonably have predicted that treatment of SLE in a subject would occur *via* administration of the soluble LTβR agents of the present invention. The present specification therefore sufficiently enables one of ordinary skill in the art to practice the methods of the present invention without undue experimentation. Applicants submit that the present specification meets the enablement requirement set forth in 35 U.S.C. 112, first paragraph, and respectfully request that the Examiner withdraw the 112, first paragraph rejection.

Rejection of Claims 51-58 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has rejected claims 51-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent Nos. 6,403,087 (herein '087) and 6,669,941 (herein '941). Applicants respectfully traverse. Allowance of the pending claims and withdrawal of the obviousness-type double patenting rejection over claims 1-14 of the '087 and '941 patents is respectfully requested.

Applicants respectfully traverse this rejection and request reconsideration and withdrawal on the grounds that claims 51-58 of the instant application are directed to patentably distinct species of treatment methods involving soluble LTβR agents. Claims 1-14 of the '087 patent encompass methods of inhibiting Th1 cell-mediated immune responses in an animal *via* administration of a soluble lymphotoxin-beta receptor (LTβR) fused to one or more heterologous protein domains. Claims 1-14 of the '941 patent encompass methods of treating a Th1 cell-associated autoimmune disease in an animal *via* administration of a soluble lymphotoxin-beta receptor (LTβR) fused to one or more heterologous protein domains. Both the '087 and '941 patents define Th1 cell-mediated immune responses to comprise immune responses associated with graft rejection and ***organ-specific autoimmune conditions*** such as multiple sclerosis, insulin-dependent diabetes, sympathetic ophthalmia, uveitis and psoriasis. Both patents further define Th1-type diseases, describing, "[s]everal systemic autoimmune diseases, including various arthritides, [to be] Th1 cell-associated. Rheumatoid arthritis and Sjorgren's syndrome both appear to involve Th0 and Th1 cells. ***In contrast, systemic lupus erythematosus (SLE) appears to have an aberrant Th0/Th2 dominated response***" (emphasis added). In contrast, claims 51-58 are directed to patentably distinct species of treatment methods comprising administration of a soluble LTβR agent for treatment of systemic lupus erythematosus (SLE) in a mammal. SLE is defined in the present application as a ***systemic autoimmune condition*** associated with "pathological humoral immune responses". The term "humoral response" is in turn defined in the present application as the "immunological response of an animal to a foreign antigen whereby the animal produces antibodies to the foreign antigen. The Th2 class of T helper cells are important to the efficient production of high affinity antibodies." Thus, SLE as defined in the claims of the present invention ***is not a Th1 disease***, but rather is characterized as possessing a Th2 component. (Indeed, a review published near the time of filing of the priority

date of the present application classifies SLE as a Th2 disease (Kroemer et al., Autoimmunity 1996, 24:25-33; enclosure).)

The Examiner additionally relies on an article by Smolen as teaching that "it is unclear whether or not SLE is in fact a TH1 or TH2 disease." Applicants submit that this article was published six years after the filing of the priority date of the instant application, thus the review fails to address the issue of SLE classification at the time of filing of the instant application. Additionally, because the review is equivocal in its classification of SLE, the review presents no basis for one of ordinary skill in the art to conclude that the SLE-directed therapeutic use of soluble LTβR agents presented in the present claims would be obvious in light of the '087 and '941 patent claims.

In conclusion, the difference in subject matter which renders pending claims 51-58 patentably distinct from claims 1-14 of the '087 and '941 patents is that the claims are directed to methods of treating SLE, a non-Th1 disease, by administration of a soluble LTβR agent. As claims 1-14 of the '087 patent and claims 1-14 of the '941 patent are directed to methods of inhibiting Th1 cell-mediated immune responses in an animal *via* administration of a soluble lymphotoxin-beta receptor (LTβR), none of the differences in subject matter recited in claims 51-58 is obvious over claims 1-14 of the '087 and '941 patents. As such, each of the pending claims 51-58 is patentably distinct over claims 1-14 of the '087 and '941 patents and it is respectfully requested that the obviousness-type double patenting rejection be reconsidered and withdrawn.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. BGNA013CN from which the undersigned is authorized to draw.

Dated: March 10, 2005

Respectfully submitted,

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